NTP
National Toxicology Program

Draft NTP Monograph on Health Effects of Low-level Lead:

Immune Effects

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Peer Review Meeting
November 17-18, 2011

Immune Effects of Low-level Pb

- Principal immune-related health effects of Pb
  - **Children**
    - Increased hypersensitivity and allergic sensitization (diagnosed by skin prick testing)
    - Supported by increased serum immunoglobulin E (IgE)
  - **Adults** – no consistent immune health effect

- ATSDR and EPA conclude
  - Pb alters immune parameters (e.g, T-cells)
  - Pb-associated functional immune changes not rigorously evaluated in humans

- Animal data support immunotoxicity of Pb

Increased Serum IgE in Children

- Elevated serum levels of IgE in children
  - IgE is primary mediator of type-I hypersensitivity
    - Associated with allergic sensitization
    - Can be associated with allergic disease such as asthma
  - Does not necessarily equate to disease

NTP Conclusions: *sufficient* evidence that blood Pb levels <10µg/dL are associated with increased serum IgE in children

Increased Serum IgE in Children - Evidence

NTP Conclusion: *sufficient* evidence <10µg/dL based on:

- 5 cross-sectional studies reporting an association between blood Pb <10µg/dL in children and elevated IgE
- **Supported by**
  - IgE associated with hair Pb in newborns (Annesi-Maesano, 2003)
  - IgE associated with Pb-dustfall in children (Heinrich, 1999; ecological study)
  - Animal data report Pb-related increases in IgE
- **Other data**
  - Similar effect at higher blood Pb levels (>10µg/dL) in a study of parental smoking, Pb and IgE in children (Hagazy, 2011)

Increased Hypersensitivity in Children

- Increased hypersensitivity responses in children
  - Allergic sensitization

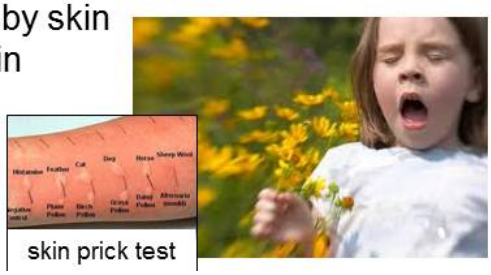
NTP Conclusion: *limited* evidence that blood Pb levels <10µg/dL are associated with increased hypersensitivity responses in children

Increased Hypersensitivity in Children – Evidence

NTP Conclusion: *limited* evidence <10µg/dL based on:

- A prospective study reporting
  - An association between maternal and cord blood Pb <10µg/dL and sensitization to common allergens
  - Diagnosed in children by skin prick testing at age 5

- **Supported in children by:**
  - Pb-related increases in serum IgE in children
  - Increased odds ratio for sensitization by skin prick test associated with Pb-dustfall in children (Heinrich, 1999; ecological study)



skin prick test

Eczema and Asthma in Children

- **Eczema**: skin inflammation with lesions that may include itching and burning
- **Asthma**: inflammatory disease of the lungs characterized by difficulty breathing

NTP Conclusion: *Inadequate* evidence of an association between blood Pb levels <10µg/dL and eczema or asthma in children

Eczema and Asthma in Children - Evidence

NTP Conclusion: *Inadequate* evidence <10µg/dL based on

- Eczema or Asthma in children
  - Few studies in children at any blood Pb level
  - **Eczema**: support limited to single group of dermatology patients
  - **Asthma**: studies generally reported lack of an association

In Adults

IgE, Hypersensitivity, Eczema, and Asthma

NTP Conclusion: *Inadequate* evidence <10µg/dL based on

- Few studies **in adults**
- Generally no association with any blood Pb levels
- **IgE**: 2 studies at much higher blood Pb (30 - 50µg/dL)

Other Immune Endpoints

NTP Conclusion: *Inadequate* evidence <10µg/dL

- Immune Endpoints:
  - Serum Immunoglobulins (IgM, IgG)
  - Antibody Response
  - T lymphocytes or T-cells
  - Monocyte/Macrophages
  - Neutrophils
  - Delayed type hypersensitivity (DTH)
- Few studies < 10µg/dL
- Inconsistent results in children and **in adults**
- At higher blood Pb levels:
  - Decreased number and % T-cells (>15µg/dL)
  - Altered Neutrophil chemotaxis (>30µg/dL)

The NTP's Conclusions for Immune Effects

There is *limited* evidence that blood Pb levels <10µg/dL are associated with adverse immune effects in children and there is *inadequate* evidence in adults.

Specific Immune Charge Questions

i. Please comment on whether the scientific evidence presented supports the NTP's conclusions.

ii. Please comment on whether you agree/disagree with the NTP's conclusions. Explain why. Identify any references that should be cited.

   a. Serum immunoglobulin E (IgE)
   b. Hypersensitivity responses and allergic sensitization diagnosed by skin prick testing
   c. Eczema and asthma
   d. Other observational or functional immune endpoints (T-cells; Macrophages; Neutrophils)

Table 5.4: NTP Conclusions on Immune effects of low level Pb – part 1 of 3				
Health Effect	**Population or Exposure Window**	**Conclusion**	**Blood Pb Evidence**	**Bone Pb Evidence**
Increased serum IgE	Prenatal	*Inadequate*	Unclear	No, but hair Pb data
	Children	*Sufficient*	Yes, <10µg/dL	No data
	Adults	*Inadequate*	Unclear	No data
Increased Hypersensitivity and Allergy (e.g., positive skin prick test)	Prenatal	*Limited*	Maternal and cord<10µg/dL	No data
	Children	*Limited*	Yes, <10µg/dL	No data
	Adults	*Inadequate*	Unclear	No data
Asthma, Eczema, etc.	Prenatal	*Inadequate*	Unclear	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear	No data

Table 5.4: NTP Conclusions on Immune effects of low level Pb – part 2 of 3				
Health Effect	**Population or Exposure Window**	**Conclusion**	**Blood Pb Evidence**	**Bone Pb Evidence**
Altered serum IgG, IgM	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear	No data
Altered antibody response	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	No data	No data
Immunophenotyping (e.g., T-cells, B-cells)	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear >15µg/dL data suggest changes in T-cells or T-cell subpopulations	No data

Table 5.4: NTP Conclusions on Immune effects of low level Pb – part 3 of 3				
Health Effect	**Population or Exposure Window**	**Conclusion**	**Blood Pb Evidence**	**Bone Pb Evidence**
Monocyte/Macrophage function	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear (one study)	No data
	Adults	*Inadequate*	Unclear	No data
Neutrophil function	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	Unclear >30µg/dL data suggest changes in chemotaxis and lytic activity	No data
Delayed type Hypersensitivity (DTH) response	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	No data	No data

e. Other immune effects

i. Please comment on whether there are additional immune effects in humans that may be adversely affected by low-level Pb exposure that you would recommend adding to the document.

Please comment on whether and how the additional immune effects would affect the overall conclusions for health effects associated with blood Pb levels <10µg/dL.

A. General Questions

1) Is the text in the draft monograph articulated clearly and correctly? Are the summary sections useful? Are the tabular information and format easily understandable? If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

2) Is the information in the draft monograph's text and tables presented objectively?
If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

Increased Serum IgE in Children - Evidence

NTP Conclusion: *sufficient* evidence <10µg/dL based on:

- Cross-sectional studies in children reporting an association between blood Pb and elevated IgE
  - Hon (2009, 2010, 2011): IgE correlated with blood Pb in children with eczema (mean 1.9µg/dL)
  - Lutz (1999): blood Pb correlated with IgE (mean not reported; 64% had blood Pb<10µg/dL)
  - Sun (2003): IgE increased in girls with blood Pb>10µg/dL

- **Supported by:**
  - Pb and IgE associated in newborns (Annesi-Maesano, 2003)
  - Blood Pb >10µg/dL associated with increased IgE in a study of effects of parental smoking (Hagazy, 2011)
  - An ecological study of Pb dustfall in children (Heinrich, 1999)
  - Animal data on Pb-related increases in IgE